Volume 20, No 1 | International Journal of Radiation Research, January 2022

Estimation of human absorbed dose of ^{68}Ga-Citrate based on biodistribution data in rats: Comparison with ^{67}Ga-Citrate

F. Habibi[1], R. Faghihi[1], S. Zolghadri[2], H. Yousefnia[2*], S. Sina[3], F. Mohammadpour-Ghazi[2]

[1]Shiraz University, Nuclear Engineering Department, Shiraz, Iran
[2]Radiation Application Research School, Nuclear Science and Technology Research Institute (NSTRI), Tehran, Iran
[3]Shiraz University, Radiation Research Center, Shiraz, Iran

► ***Original article***

***Corresponding author:**
Hassan Yousefnia, Ph.D.,
E-mail:
hyousefnia@aeoi.org.ir

Received: August 2020
Final revised: June 2021
Accepted: July 2021

Int. J. Radiat. Res., January 2022; 20(1): 151-156

DOI: 10.52547/ijrr.20.1.23

Keywords: *Internal radiation dose, MIRD, ^{68}Ga-citrate, ^{67}Ga-citrate.*

ABSTRACT

Background: In recent years, Gallium-68 citrate has become known as an alternative radioisotope in nuclear medicine. As for its influences, ^{68}Ga-based tracers have already been proposed as agents for positron emission tomography. In this research, the values of human absorbed dose for ^{68}Ga-citrate and ^{67}Ga-citrate were estimated using the medical internal radiation dose method based on biodistribution data in rats. ***Materials and Methods***: ^{68}Ga/^{67}Ga-citrate was prepared from eluted ^{68}Ga/^{67}Ga-Cl_3 - and sodium citrate under multiple reaction forms. The biodistribution of ^{68}Ga/^{67}Ga–citrate radiolabeled compounds was investigated by dissection of five male rats at specific times after injection. The organs of the rats were removed and counted. Percentage of injected dose per gram was determined for each rat organ and the human absorbed dose was extrapolated using the rats' data. ***Results***: The results of estimating the human absorbed dose illustrate that ^{68}Ga-citrate caused a much lower human absorbed dose compared with ^{67}Ga-citrate. ***Conclusion***: According to the results, it may be concluded that ^{68}Ga-citrate, despite the better quality of PET imaging, is much safer in terms of absorption dose compared with ^{67}Ga--citrate, and from this point of view, it is a more appropriate agent for imaging applications.

INTRODUCTION

^{67}Ga-citrate, as an imaging agent, has been consumed for the recognition of infections and inflammations for several decades [1]. Citrate is one of the major substrates for intracellular metabolism and ^{67}Ga-citrate is absorbed in inflammation regions, thus it can be used as a diagnostic agent in many diseases like autoimmune-based inflammations or chronic pancreatitis. It can also be used in the detection of some malignancies including Hodgkin's disease, lymphomas, and bronchogenic carcinoma [2].

With the increasing progress in the production of positron emission tomography (PET) for over the past 30 years, interest in the use of positron emission radionuclides has increased. Accordingly, ^{68}Ga and ^{18}F can be used as alternatives in nuclear imaging. Physical properties and cyclotron-independent availability of gallium-68 from ^{68}Ge/^{68}Ga generator with low cost led to gallium-68 being proposed as a new PET element [3].

^{68}Ga decays to an excited state at 1077 keV (3%) and has a half-life of 67.71 minutes[4]. In spite of the significant use of ^{18}F as a PET radionuclide, $^{68}Ga^{3+}$ seems more susceptible for labeling due to its chemical characteristic. ^{68}Ga half-life is suitable in coupling with many peptides and also some small molecules due to better target localization and rapid blood clearance [5]. Also, ^{68}Ga-based tracers have been found more effective than ^{18}F-based agents and interested in ^{68}Ga infection and other ^{68}Ga based tracer studies [6-8].

Like lymphocytes and macrophages, gallium attachment to tissues is mediated by lactoferrin. According to the recent studies, ^{68}Ga-chloride possibly can use for monitoring of bone healing in experimental osteomyelitis. After the development of ^{68}Ga generators, researchers focused on the production and utilization of ^{68}Ga-citrate for infection studies. Some preliminary data demonstrated the potential use of ^{68}Ga-citrate for diagnosis of skeletal muscle inflammation and infection, or tuberculosis (TB), abdominal infection, and contagious disease [9].

Despite the promising results of ^{68}Ga-citrate in the imaging of infections and inflammations, the absorbed dose of this radiotracer in clinical trials was not reported in the literature. Estimation of the absorbed dose is an important step for developing of new radiopharmaceuticals and can help to assess the maximum amount of activity that should be undertaken [10, 11]. Medical internal radiation dose (MIRD) is a well-developed system for estimation of

[DOI: 10.52547/ijrr.20.1.23]

human organ's absorbed dose that can be combined with the measured animal's organ's doses [12-14].

This study aimed to estimate the human organ absorbed dose after the injection of ^{68}Ga-citrate and compare this new radiotracer from the dosimetry perspective with ^{67}Ga-citrate, which has been commonly used in clinical studies for several decades. For this purpose, ^{68}Ga/^{67}Ga-citrate was prepared and the biodistribution of ^{68}Ga/^{67}Ga–citrate radiolabeled compounds were assessed in male rats and finally, the human radiation absorbed dose was extrapolated according to the rats' data.

MATERIALS AND METHODS

50 mCi ^{68}Ge/^{68}Ga generator was provided from internal resource (Pars Isotope Co., Tehran, Iran). Sigma Aldrich (USA) was considered to obtain all chemical reagents. Radionuclide purity was assessed using a high purity germanium (model GC1020-7500SL, Canberra Industries Inc, USA) and radiochemical purity was investigated by a AR-2000 radio TLC scanner instrument (Bio scan, Europe Ltd CO., France). Wild-type 18-week old male rats were prepared from the Pasteur Institute (Iran). All rats were kept at routine day/night light program. United Kingdom Biological Council's Guidelines were used for animal studies [15]. NSTRI Ethical Committee approval was obtained for conducting the research. Student T-test was utilized for statistical analysis (statistical significance; $P<0.05$). The values were expressed as the mean ± standard deviation (Mean ± SD).

Preparation and quality control of ^{68}Ga-citrate and ^{67}Ga-citrate

About 3-5 mCi of $^{68}GaCl_3$ was washed by 150 µL of 0.6 M metal-free HCL, and poured into a 5 mL borosilicate vial and dried through heating and N_2 gas. 300 µL of 0.1 M sodium citrate was added and shaken for 15 min at 50 ˚C. For radiochemical purity checking, a 5 µL spot of the sample was used on a Whatman No. 2 paper and 0.4 M sodium acetate: methanol (7:3) mixture was considered as the mobile phase. HPLC was performed under the following conditions: a gradient of water and acetonitrile with the volume proportion of 3:2 as the eluent; flow rate of 1.5 ml/min; pressure of 130 psi; reversed-phase Whatman Partsphere C_{18} column for 15 min. Finally, the ultimate solution with appropriate chemical purity was sterilized by filtering, and pH was adjusted on 5.5-7.

^{67}Ga was prepared through ^{68}Zn (p, 2n)^{67}Ga reaction at 30 MeV cyclotron (cyclotron-30,IBA). To remove the other impurities, radiochemical separation was performed according to the previously reported literature [16]. Ga-67 was eluted in the form of [^{67}Ga] $GaCl_3$. 100 mg of sodium citrate was added to the final solution (25 mL, 50-250 mCi) and was transferred to a buffering flask for about 10 minutes. Then filtration was performed through a 0.22-micron membrane.

Biodistribution studies of ^{67}Ga/^{68}Ga-citrate in rats

100 µL of the radiolabeled complexes were injected into the wild-type 18 week's male rats. The total amount of injected radioactivity was measured by counting the syringes before and after injection into a dose calibrator with the same geometry. CO_2 asphyxiation was utilized to kill the five rats at each specified intervals after injection (3, 24, 48, 72, and 96 h for ^{67}Ga-citrate and 15, 30, 45, 60, and 120 min for ^{68}Ga-citrate). The main organs were removed and weighed and the specific activities were determined by an equipped HPGe detector utilizing equation 1:

$$A = \frac{N}{\varepsilon \gamma ts\, k1\, k2\, k3\, k4\, k5} \quad (1)$$

Where, ε is the energy efficiency for gamma photopeak, γ is the gamma emission probability, t_s is the sample spectrum collection life time (in seconds), k1, k2, k3, k4 and k5 are the correction factors of the measurements. N is the corrected net peak area of the photopeak given by equation 2:

$$N = Ns\frac{ts}{tb}\, Nb \quad (2)$$

Where; Ns is the net peak area, N_b is the background net peak area, ts is the background spectrum collection live time (in seconds). Eventually, the non-decay corrected %ID/g was calculated for any organ.

The ^{67}Ga/^{68}Ga activity concentration was normalized to the weight of the tissue and expressed as % ID/g (t) that can be easily found by using equation 3:

$$\%ID/g = \frac{A_{tissue}/M_{tissue}}{A_{total}} \times 100 \quad (3)$$

Where A_{tissue} is the activity of ^{67}Ga/^{68}Ga in the sample, M_{tissue} is the sample mass e and A_{Total} is the total injected activity of ^{67}Ga/^{68}Ga into the rat [17, 18].

Human organs accumulation activity

Non-decay-corrected time-activity curves of the different organs were plotted to calculate the accumulated ^{67}Ga/^{68}Ga activity by calculating the area under the graphs. Thus the data points that define the percentage-injected dose were fitted to the uptake and clearance curve [19, 20].

Moreover, graphs were extrapolated to infinity by fitting the endpoint of each graph to a mono-exponential curve. Then the total area underneath the chart was aggregated. To prevent the under-sampling region of below the graph, we calculated the AUCs (the area under curves) when the R^2 square of fitted curves was higher than 0.9 for each organ. Although 15 organs were available, only 11 organs were used as source organs which are

[DOI: 10.52547/ijrr.20.1.23]

mentioned in MIRD for calculation of AUCs.

For extrapolation of animals' organ uptake data to the humans' equivalent uptake, Sparks and Aydogan method was used and the cumulated activity was calculated utilizing equation 4:

$$\tilde{A}_{\text{Human organ}} = \tilde{A}_{\text{Animal organ}} \times \frac{\text{Organ mass}_{\text{Human}}/\text{Body mass}_{\text{human}}}{\text{Organ mass}_{\text{animal}}/\text{Body mass}_{\text{animal}}} \quad (4)$$

Absorbed dose calculation

The absorbed dose of each human organ was computed by MIRD method using equation 5:

$$\tilde{D}(r_k) = \sum_h \tilde{A}_h \, S(r_k \leftarrow r_h) \quad (5)$$

Where $\tilde{D}(r_k)$ describes the organ absorbed dose and $\tilde{A}_h$ is the accumulated activity in the source organs. the value of S(rk←rh) will depend on the physical decay characteristics of the radioisotopes, the organ size and the range of the emitted radiations [21], which is called the S factor. The value of S factors is taken from http://doseinfo-radar.com/ RADAR-phan.html [22].

Calculation of effective absorbed dose

The effective absorbed dose was determined for each organ by employing equation 6:

$$E=\sum_T W_T H_T \quad (6)$$

Where, W_T is the tissue-weighting factor presented in ICRP 106 and H_T is the equivalent dose in a tissue or organ [23].

Statistical analysis

Statistical Package for Social Sciences (SPSS) software was used for data analysis. To express all values as mean ±standard deviation, five rats were used for any interval. The data were calculated and Student T-test was utilized for statistical analysis (statistical significance; P<0.05).

RESULTS

Optimization test of the radiolabeled complexes

Because of the short half-life of ^{68}Ga, a rapid radiolabeling procedure is required to perform time, pH and temperature optimization studies. The optimized temperature was detected as 85-90 ˚C because, in a significant specific activity of the freshly milked ^{68}Ga fraction, all the radio-gallium converted to the desired complex at this temperature, while the radiolabeling reaction for ^{67}Ga-citrate started at room temperature and was completed by applying heat. According to the results, the solution of ^{68}Ga-citrate with reasonable radiochemical purity was sterile filtered, and pH was adjusted to 5.5-7. A single peak in the ITLC method was considered to designate the free remained gallium. The solid phase extraction method helped to obtain high radiochemical purity for tracer (>97 %). The possibility of performing the biological experiments was provided through the stability of the solution at room temperature for two hours.

Biodistribution of ^{67}Ga/^{68}Ga-citrate in rats

The distribution of ^{67}Ga/^{68}Ga-citrate (15 to 120 min for ^{68}Ga-citrate and 3 to 96 h for ^{67}Ga-citrate) was ascertained using wild-type rats. The biodistribution data of ^{67}Ga-citrate up to 96 h and biodistribution of ^{68}Ga-citrate up to 2h after injection in rat's organs are shown in tables 1 and 2 respectively. The highest biodistribution for both compounds is allocated to blood and the majority of the labeled compound was cleaned from the blood rapidly. Moreover, the second-highest biodistribution for 67Ga-citrate is related to the liver which is 1.123%, while the spleen in ^{68}Ga-citrate is detected as the second-highest one with an amount of 0.112%.

As shown in figure 1 (Biodistribution of ^{67}Ga-citrate), the clearance curve of the liver showed a downward trend through 96 hours, whereas the spleen increased until 72 h and hit a through in the last interval. Regarding figure 2 (Biodistribution of ^{68}Ga-citrate), although the liver had a rapid decrease in ID/g during the first 30 min interval, it decreased slightly after that time. In addition, the spleen had an upward trend in ID/g during the 45 min, and then it decreased gradually.

MIRD dose calculation

Following the injection of 14-M--Bq ^{68}Ga-citrate into the rat, the effective absorbed human dose was estimated through the Spark method. As represented in table 3, the highest effective absorbed dose for ^{68}Ga -citrate was in the lungs with 0.0041 mSv/MBq and the liver and spleen with 0.0025 and 0.0020 mSv/ MBq, respectively.

Table 1. Biodistribution of ^{67}Ga-citrate at different time points (represented as injected dose per gram) decay uncorrected data.

	3 h	24 h	48 h	72 h	96 h
Blood	1.340± 0.121	0.019± 0.002	0.396± 0.028	0.033± 0.001	0.007± 0.000
Heart	0.409± 0.062	0.065± 0.003	0.101± 0.007	0.048± 0.002	0.006± 0.001
Lung	0.888± 0.091	0.023± 0.002	0.236± 0.016	0.093± 0.004	0.011± 0.001
Skin	0.312± 0.043	0.025± 0.001	0.134± 0.006	0.086± 0.006	0.003± 0.000
Stomach	0.453± 0.021	0.152± 0.007	0.212± 0.010	0.074± 0.004	0.013± 0.001
Intestine	0.938± 0.067	0.037± 0.001	0.660± 0.032	0.104± 0.005	0.035± 0.001
Liver	1.123± 0.201	0.738± 0.032	0.817± 0.035	1.706± 0.158	0.071± 0.003
Spleen	0.921± 0.084	0.624± 0.054	0.979± 0.058	1.127± 0.136	0.089± 0.003
Kidney	0.838± 0.067	0.400± 0.021	0.757± 0.047	0.220± 0.013	0.050± 0.002
Muscle	0.208± 0.037	0.052± 0.002	0.107± 0.007	0.047± 0.001	0.017± 0.001
Bone	0.618± 0.052	0.189± 0.031	0.607± 0.043	0.532± 0.034	0.029± 0.001

[DOI: 10.52547/ijrr.20.1.23]

Table 2. Biodistribution of ^{68}Ga-citrate at different time points (represented as injected dose per gram) decay uncorrected data.

	15 min	30 min	45 min	60 min	120 min
Blood	0.276± 0.030	0.132± 0.021	0.126± 0.014	0.083± 0.005	0.060± 0.003
Heart	0.076± 0.004	0.057± 0.003	0.042± 0.003	0.037± 0.001	0.026± 0.001
Lung	0.021± 0.001	0.171± 0.036	0.174± 0.027	0.145± 0.012	0.055± 0.003
Skin	0.031± 0.001	0.029± 0.001	0.021± 0.003	0.013± 0.001	0.008± 0.000
Stomach	0.027± 0.001	0.024± 0.002	0.017± 0.002	0.015± 0.000	0.008± 0.000
Intestine	0.030± 0.002	0.027± 0.001	0.024± 0.001	0.024± 0.001	0.020± 0.001
Liver	0.078± 0.002	0.096± 0.009	0.100± 0.007	0.061± 0.003	0.020± 0.001
Spleen	0.112± 0.008	0.052± 0.003	0.038± 0.002	0.037± 0.002	0.013± 0.000
Kidney	0.050± 0.003	0.043± 0.002	0.026± 0.001	0.022± 0.001	0.020± 0.001
Muscle	0.021± 0.001	0.026± 0.001	0.022± 0.001	0.018± 0.001	0.014± 0.001
Bone	0.032± 0.001	0.028± 0.003	0.023± 0.001	0.021± 0.001	0.019± 0.001

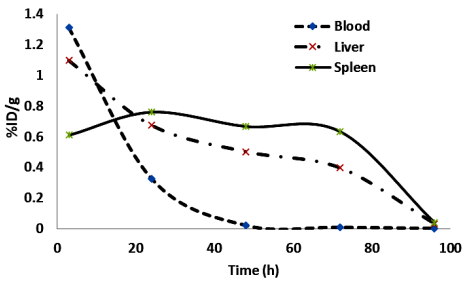

Figure 1. The non-decay-corrected clearance curves from blood, liver, and spleen of the rat after i.v. injection of ^{67}Ga-citrate. The X axis displays time as minutes post injection. The Y-axis displays the mean decay uncorrected values as the percentage of injected activity per gram (% ID/g).

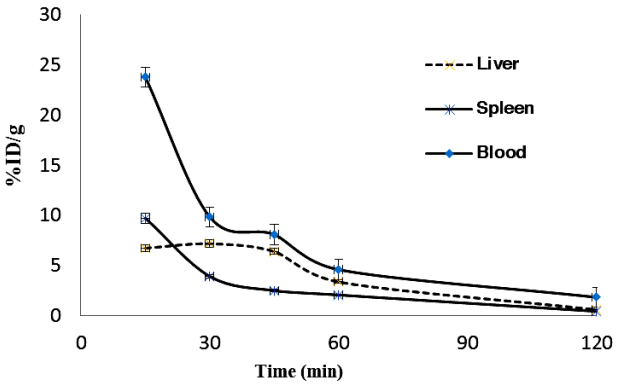

Figure 2. The non-decay-corrected clearance curves from liver, spleen, and blood of the rat after i.v. injection of 68Ga-citrate. The X is time as post injection minutes. The Y-axis shows the mean decay uncorrected values as the percentage of administered activity per gram (% ID/g).

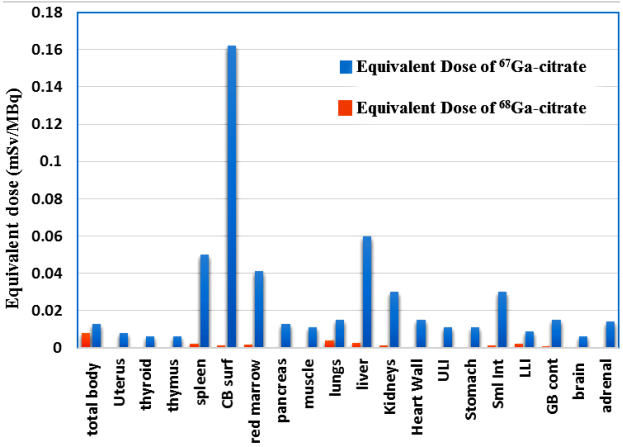

Figure 3. Comparison of equivalent absorbed dose prediction of 67Ga/68Ga-citrate in humans based on biodistribution data in rats.

Table 3. Estimation of human absorbed dose from rat data after i.v. administration of 67Ga/68Ga-citrate.

	^{67}Ga-citrate		^{68}Ga-citrate	
	Equivalent dose in humans (mSv/MBq)	Effective dose in humans (mSv/MBq)	Equivalent dose in humans (mSv/MBq)	Effective dose in humans (mSv/MBq)
Target organ				
Adrenal	0.0140±	2E-3	0.0003	4E-5
Brain	0.0060	6E-3	0.0001	1E-6
GB count	0.0150	2E-3	0.0010	1E-5
LLI	0.0090	1E-3	0.0020	2E-4
Sml Int	0.0300	4E-4	0.0015	2E-4
Stomach	0.0110	1E-3	0.0004	5E-5
ULI	0.0110	1E-3	0.0003	4E-5
Heart Wall	0.0150	2E-3	0.0002	2E-5
Kidneys	0.0300	4E-4	0.0012	1E-4
Liver	0.0600	2E-3	0.0025	1E-4
Lungs	0.0150	2E-3	0.0041	5E-4
Muscle	0.0110	1E-3	0.0001	1E-5
Pancreas	0.0130	1E-3	0.0003	4E-5
Red marrow	0.0410	5E-3	0.0016	2E-4
CB surf	0.1620	2E-3	0.0015	1E-5
Spleen	0.0500	6E-3	0.0020	2E-5
Thymus	0.0060	7E-3	0.0002	2E-5
Thyroid	0.0060	2E-4	0.0002	8E-6
Uterus	0.0080	1E-3	0.0002	2E-5
Total body	0.0130	13E-3	0.0080	8E-3

Tissue-weighting factors according to international commission on radiological protection ICRP 103 (ICRP 2007). *LLI: lower large intestine, **Int: intestine and content, ***ULI: upper large intestine

DISCUSSION

In this research study, concerning the advantages of PET in nuclear imaging and promising results of ^{68}Ga-citrate in imaging of infections, an attempt was made to compute the absorbed dose of this new imaging agent and compare it with the most common and old used radiopharmaceutical for this purpose, ^{67}Ga-citrate, from the dose point of view.

For this purpose, ^{68}Ga/^{67}Ga–citrate complexes were prepared according to the previously reported

[DOI: 10.52547/ijrr.20.1.23]

literature [24, 25]. The biodistribution data of both complexes were assessed in wild-type male rats. The biodistribution data of both complexes demonstrated high accumulation in the lung, liver and the spleen. According to the placement of macrophage cells in reticuloendothelial organs like spleen and lung and the well-known mechanism of Ga accumulation in macrophage cells [26], accumulation of ^{68}Ga/^{67}Ga–citrate in these organs can be justified. The biodistribution data are under the other research [24].

The absorbed dose of human organs was calculated based on the biodistribution data in rat organs and by using the mass extrapolation method. It should be considered that the distribution of a radiopharmaceutical changes from rodents to humans [27]. However, the extrapolation from animal to human can lead to overestimations or underestimations [28], estimation of absorbed dose based on rodents is the first step in the development of radiopharmaceuticals and previous studies have demonstrated the efficacy of utilizing animal biodistribution as a model for estimations of human absorbed dose [29].

The results of absorbed dose calculation indicated higher dose delivery in human organs after injection of ^{67}Ga-citrate in comparison with ^{68}Ga-citrate. This issue is consistent with previous results evaluating the absorbed dose of ^{68}Ga-ECC and ^{67}Ga-ECC [30]. This discrepancy in the absorbed dose of the complexes is related to the physical half-live of the radionuclides and the decay modes. Since the physical half-life of ^{67}Ga is about seventy times higher than ^{68}Ga and besides that ^{67}Ga decays by emitting ten gammas and fifteen X-rays, it leads to higher doses in the organs.

The results show that the lungs, liver, and spleen received the highest equivalent absorbed dose after injection of ^{68}Ga-citrate with 0.0041, 0.0025, and 0.0020 mSv/MBq, respectively. However, the highest equivalent absorbed dose was seen in CB surface, liver and spleen with 0.1620, 0.0600 and 0.0500 mSv/MBq, respectively, after injection of 67Ga-citrate. The clearance curves of ^{68}Ga/^{67}Ga–citrate complexes were almost similar, but the difference values of the S factors caused the discrepancies in organs that received the highest adsorption dose. This diversity has also been observed in previous research [30].

CONCLUSION

In this study, the absorbed dose of ^{67}Ga-citrate and ^{68}Ga-citrate in human organs were calculated based on biodistribution data in wild-type rats. The organs with the highest accumulated activity were the lung, spleen, and liver. The total body equivalent absorbed dose was calculated as 0.013 and 0.008 mSv/MBq after injection of ^{67}Ga-citrate and ^{68}Ga-citrate, respectively. According to the results, all organs receive about 10 times more absorbed dose after ^{67}Ga- citrate injection than ^{68}Ga-citrate. Generally, ^{68}Ga-citrate can be a better candidate for imaging of infections and inflammation in the dose delivery aspect.

ACKNOWLEDGMENTS

The authors would like to acknowledge the NSTRI for the support of this study.

***Ethical approval*:** The approval of the NSTRI Ethical Committee was obtained for conducting this research.

***Conflict of interest*:** There is no conflict of interest.

***Funding sources*:** This study was funded by the NSTRI.

***Author contribution*:** All the authors contributed in all the parts of the study.

REFERENCES

1. Burleson RL, Johnson MC, Head H (1973) Scintigraphic demonstration of experimental abscesses with intravenous ^{67}Ga citrate and ^{67}Ga labeled blood leukocytes. *Ann Surg, **178**: 446–452*.
2. Bitterman PB, Rennard SI, Keogh BA, Wewers MD, Adelberg S, Crystal RG (1986) Familial idiopathic pulmonary fibrosis. *N Engl J Med, **314**: 1343-1347*.
3. Shanehsazzadeh S, Lahooti A, Yousefnia H, Geramifar P, Jalilian AR (2015). Comparison of estimated human dose of (68)Ga-MAA with (99m)Tc-MAA based on rat data. *Ann Nucl Med, **29**: 745-753*.
4. Firestone RB and Shirley VS (1998) Table of isotopes, Update 8th Edition.
5. Breeman WA and Verbruggen AM (2007) The 68Ge/68Ga generator has high potential, but when can we use 68Ga-labelled tracers in clinical routine? *Eur J Nucl Med Mol Imaging, **34**: 978-981*.
6. Fellner M, Baum RP, Kubíček V, Hermann P, Lukeš I, Prasad V, Rösch F (2010) PET/CT imaging of osteoblastic bone metastases with 68Ga-bisphosphonates: first human study. *Eur J Nucl Med Mol Imaging, **37**: 834*.
7. Kratochwil C, Giesel FL, López-Benítez R, Schimpfky N, Kunze K, Eisenhut M, *et al.* (2010) Intraindividual comparison of selective arterial versus venous 68Ga-DOTATOC PET/CT in patients with gastroenteropancreatic neuroendocrine tumors. *Clin Cancer Res, **16**: 2899-2905*.
8. Yang DJ, Kim EE, Inoue T (2006) Targeted molecular imaging in oncology. *Ann Nucl Med, **20**(1): p. 1*.
9. Xu T and Chen Y (2020) Research progress of [68Ga]Citrate PET's utility in infection and inflammation Cmaging: a Review. *Mol Imaging Biol, **22**: 22–32*.
10. Rabiei A, Shamsaei M , Yousefnia H , Jalilian AR (2018) Pharmacokinetic studies and human absorbed dose estimation of 68Ga-(4 {[(bis (phosphonomethyl)) carbamoyl] methyl}-7, 10-bis (carboxymethy l)-1, 4, 7, 10-tetraazacyclododec-1-yl) acetic acid. *Int J Radiat Res, **16**: 473-480*.
11. Yousefnia H, Zolghadri S, Jalilian A, Naseri Z (2015) Preliminary absorbed dose evaluation of two novel ^{153}Sm bone-seeking agents for radiotherapy of bone metastases: comparison with ^{153}Sm-EDTMP. *J Radiother Pract, **14**: 252-259*.
12. Sparks R and Aydogan B (1999) Comparison of the effectiveness of some common animal data scaling techniques in estimating human radiation dose. Proceedings of the Sixth International Radiopharmaceutical Dosimetry Symposium, Oak Ridge TN. Oak Ridge Associated Universities, *705–716*.
13. Stabin, MG, Tagesson M, Thomas SR, Ljungberg M, Strand SE (1999) Radiation dosimetry in nuclear medicine. *Appl Radiat Isot, **50**: 73-87*.
14. Stabin MG (2008) The importance of patient-specific dose calculations in nuclear medicine. *Nuclear Engineering and Technology, **40**: 527-532*.
15. Biological Council (1987) Guidelines on the use of living animals in scientific investigations. Biological Council, UK, 2nd edn.

[DOI: 10.52547/ijrr.20.1.23]

16. Jalilian AR, Yousefnia H, Shafaii K, Novinrouz A, Rajamand AA (2012) Preparation and biodistribution studies of a radiogallium-acetylacetonate bis (thiosemicarbazone) complex in tumor-bearing rodents. *Iran J Pharm Res,* ***11****: 523-531*.
17. Jalilian A, Shanehsazzadeh S, Akhlaghi M, Kamalidehghan M, Moradkhani S (2010) Development of [^{111}In]-DTPA-buserelin for GnRH receptor studies. *Radiochim Acta,* ***98****: 113-119*.
18. Jalilian AR, Rowshanfarzad P , Bolourinovin F, Kamalidehghan M, Majdabadi A, Moradkhani S (2008) Biodistribution study of [61Cu] pyruvaldehyde-bis (N-4-methylthiosemicarbazone) in normal rats as a PET tracer. *Nucl Sci Tech,* ***19****: 159-164*.
19. Khorrami Moghaddam A, Jalilian AR, Hayati V, Shanehsazzadeh S (2010) Determination of human absorbed dose of 201Tl (III)-DTPA-HIgG based on biodistribution data in rats. *Radiat Prot Dosimetry,* ***141****: 269-274*.
20. Shanehsazzadeh S, Lahooti A, Shirmardi SP, Erfani M (2015) Comparison of estimated human effective dose of 67Ga-and 99mTc-labeled bombesin based on distribution data in mice. *J Radioanal Nucl Chem,* ***305****: 513-520*.
21. Snyder W, Ford MR, Warner GG, Watson SB (1975) " S" absorbed dose per unit cumulated activity for selected radionuclides and organs. *MIRD Pamphlet no. 11*.
22. Bevelacqua J (2005) Internal dosimetry primer. *Radiation Protection Management,* ***22****: 7*.
23. Valentin J (1988) Radiation dose to patients from radiopharmaceuticals (Addendum 2 to ICRP Publication 53), ICRP Publication 80. Ann. ICRP, 28.
24. Aghanejad A, Jalilian AR, Ardaneh K, Bolourinovin F, Bahrami Samani A (2015) Preparation and Quality Control of ^{68}Ga-Citrate for PET Applications. *Asia Ocean J Nucl Med Biol,* ***3****: 99–106*.
25. Jalilian AR, Novinrooz A, Motamedi-Sedeh F, Moradkhani S, Rajamand AR, Solati J (2009) Evaluation of [67Ga] citrate in the detection of various microorganism infections in animal models. *IJNM,* ***17****: 34-41*.
26. Kamada M (1987) Distribution of 67Ga-citrate in tumor tissues and various organs. (Tokyo) *Radioisotopes,* ***27****: 390–396*.
27. de Jong M, Breeman WA, Bernard BF, Bakker WH, Schaar M, van Gameren A, *et al.* (2001) [^{177}Lu-DOTA0, Tyr3] octreotate for somatostatin receptor-targeted radionuclide therapy. *Int J Cancer,* ***92****: 628–633*.
28. Boutaleb S, Pouget JP, Hindorf C, Pelegrin A, Barbet J, Kotzki PO, *et al.* (2009) Impact of mouse model on preclinical dosimetry in targeted radionuclide therapy. *Proc IEEE,* ***97****: 2076–2085*.
29. International Commission on Radiological Protection (1993) Radiological protection in biomedical research. ICRP publication 62. Stockholm, Sweden: ICRP; 1993.
30. Shanehsazzadeh S, Yousefnia H, Jalilian AR, Zolghadri S, Lahooti A (2015) Estimated human absorbed dose for (68)Ga-ECC based on mice data: comparison with (67)Ga-ECC. *Ann Nucl Med,* ***29****: 475-481*.

[DOI: 10.52547/ijrr.20.1.23]